The effect of high-dose nitroglycerin on the cerebral saturation and renal function in cardiac surgery: A propensity score analysis

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Abstract

Background: The aim of the study was to evaluate the effects of high-dose nitroglycerine administered during cardiopulmonary bypass on the intraoperative cerebral saturation and postoperative serum creatinine concentration in cardiac surgery.

Methods: In a retrospective cohort study, a total of 239 patients undergoing cardiac surgery with cardiopulmonary bypass at a tertiary medical center were included. General anesthesia consisted of volatile anesthetic and either intravenous loading of high-dose nitroglycerin (infusion rate 10 to 20 mg·h⁻¹ with a total dose of ≥0.5 mg·kg⁻¹) starting from rewarming of cardiopulmonary bypass throughout the postby-pass interval may induce hypotension and hemodilution in cardiac surgical patients. Cerebral saturation and renal function were well maintained without increasing the risk of stroke and renal replacement therapy after cardiac surgery with cardiopulmonary bypass.

Results: Patients receiving high-dose nitroglycerin had significantly lower mean arterial pressure and hematocrit levels during and after cardiopulmonary bypass. The risk of intraoperative cerebral desaturation was left-sided 23.9% versus 38.5% (p = 0.029), right-sided 29.1% versus 35.7% in the NTG and control groups, respectively. The risk of new-onset stroke and postoperative dialysis was 2.1% versus 6.3% and 1.0% versus 3.5% in the NTG and control groups, respectively.

Conclusion: An infusion of high-dose nitroglycerin initiating at rewarming of cardiopulmonary bypass and throughout the postby-pass interval may induce hypotension and hemodilution in cardiac surgical patients. Cerebral saturation and renal function were well maintained without increasing the risk of stroke and renal replacement therapy after cardiac surgery with cardiopulmonary bypass.

Keywords: Acute kidney injury; Cardiopulmonary bypass; Cerebral desaturation; Nitroglycerin

1. INTRODUCTION

Cardiopulmonary bypass (CPB) is associated with multiple significant circulatory disturbances, including hypotension, hemodilution, hypothermia, nonpulsatile blood flow, and microemboli. During CPB, endothelial cell dysfunction precipitates significant circulatory disturbances, including hypotension, hemodilution, hypothermia, nonpulsatile blood flow, and microemboli. During CPB, endothelial cell dysfunction precipitates a decrease in the production of endogenous nitric oxide (NO), compromising significantly both vascular tone and tissue perfusion.1 End-organ hypoperfusion and inherent ischemia are common in the setting of extracorporeal circulation; brain and kidneys are among the most vulnerable organs to the devastating complications.2,3

In addition, although the risk of overt postoperative stroke has decreased from 1.6% to 1.2% in cardiac surgeries since the 1980s,4 the impact of overt stroke is profound in terms of worse-adjusted hospital outcomes, longer postoperative hospital stays, and poorer downstream survival.4 In addition to microemboli, cerebral hypoperfusion is a major risk factor for brain injury or dysfunction after cardiac surgery, particularly in patients with cerebrovascular disease.5 The inflammatory response to surgery and CPB further contribute to cerebral dysfunction.

The incidence of acute renal failure requiring renal replacement therapy (RRT) after uncomplicated cardiac surgery in patients with earlier normal renal function is infrequent (<2%).6 However, the incidence of acute kidney injury (AKI) defined by consensus definitions is about 20%–30%.6,7 AKI requiring RRT after cardiac surgery has a profound impact on mortality, and even mild forms of AKI are consistently associated with later development of chronic kidney disease, multiorgan dysfunction, increased mortality, length of stay, and hospital costs.5,9

Administration of intravenous NTG has been proposed to protect against ischemia–reperfusion injuries in a limited number of studies through the mechanism of NO-induced vasodilatation.10 Intravenous NTG also reproduces the effect of endogenous late preconditioning.11 Nonetheless, effective tissue perfusion can be compromised if blood pressure falls excessively...
under the vasodilatory effect of NTG. Considering the effect of high-dose NTG on the risk of cerebral desaturation and renal injury is relatively underexplored, we conducted this retrospective cohort study applying propensity score analysis to investigate the changes in the intraoperative cerebral saturation and postoperative serum creatinine concentration after the treatment of high-dose NTG starting at rewarming phase of CPB in cardiac surgery.

2. METHODS

2.1. Study setting

The study was approved by the medical ethics committee of Taipei Veterans General Hospital, Taipei, Taiwan (TVGHIRB No. 2015-12-018CC). Written informed consent was waived, and all the study materials were anonymized and de-identified before analysis.

At the tertiary medical center, patients undergoing cardiac surgery were frequently given intravenous NTG for the cardio-protective effect. In the past, the regimen of NTG was continuous, and intravenous bolus or continuous infusion of NTG was given to elevate the systemic blood pressure. A new protocol of NTG treatment was adopted from July 2014 onwards after a review of current literature. There was no significant change in surgical or anesthetic facilities during the study period. The data of the study had been used partly in the authors’ earlier work.12

2.2. Anesthetic management

For each patient undergoing cardiac surgery, serum creatinine concentration was tested 1 day before the surgery. At the operation room, cerebral oximeters (INVOS, Medtronic, MN, USA) were used to measure and record the bilateral cerebral saturation of surgical patients in real time. Baseline cerebral saturation was obtained before anesthetic induction under room air if patients had no cardiopulmonary distress. Patients were given fentanyl 1–2 µg·kg−1 and propofol 1–1.5 mg·kg−1 for induction, and neuromuscular blocking agents to facilitate tracheal intubation with rocuronium 0.8 mg·kg−1 or cisatracurium 0.2 mg·kg−1. During anesthetic maintenance, fentanyl 50–100 µg was given before sternotomy and aortic cannulation. Anesthesia was maintained with sevoflurane 2–3 vol% or desflurane 6–8 vol% in oxygen, with a fraction of inspired oxygen of 0.6–1.0 at the anesthesiologist’s discretion. Arterial blood gas was tested each 5–10 minutes during CPB and 15–30 minutes during other phases of cardiac surgery.

2.3. Protocol of NTG loading

Intravenous administration of NTG was initiated at the rewarming of CPB with an infusion rate of 10 to 20 mg·h−1 and tapered to 5 to 10 mg·h−1 after weaning from CPB. The range of targeted MAP was 40 to 60 mmHg. If MAP was <40 mm Hg or cerebral oxygen saturation decreased to <80% of the baseline value, the MAP would be targeted accordingly. Typically, NTG was given in a total dose of >0.5 mg·kg−1 during the surgery. Fluids and blood products were first used to maintain systemic blood pressure instead of vasopressors. If cardiac index (CI) was <2.4 l·min−1·m−2, dopamine (3–10 µg·kg−1·min−1) was first given instead of epinephrine or norepinephrine. Milrinone (0.3–1.0 µg·kg−1·min−1) was used at the anesthesiologists’ discretion. After weaning from CPB, the infusion rate of NTG was adjusted by the physician of the intensive care unit (ICU) based on patients’ hemodynamics. NTG was typically discontinued within 24 hours after surgery.

2.4. Techniques of cardiopulmonary bypass

HL-30 (Maquet, Rastatt, Germany) roller pumps and Affinity NT (Medtronic, Fridley, MN, USA) oxygenators were used for all patients. Infusion of cardioplegic solutions 15°C to 29°C Custodiol HTK (Koehler Chemi, Alsbach-Haenlein, Germany) or blood (blood to crystalloid ratio 4:1) were performed. The pump flow was an adjusted output of 2.2 l·m−2 of body surface area. The pump flow was decreased to 0.5 l·min−1 in aortic clamping and unclamping. Core temperature was maintained between 32°C and 34°C in valve surgeries and allowed to drift to 34°C in coronary artery bypass grafting (CABG). When the systemic temperature was >36°C, weaning from CPB was attempted.

2.5. Selection criteria of patients

In a review of the anesthetic records of cardiac surgical patients, we included the adult patients undergoing either or both CABG and valve surgery at Taipei Veterans General Hospital between May 2012 and November 2015. Exclusion criteria were emergent surgeries, off-pump surgery, patients with history of preoperative dialysis or congenital heart diseases, and patients with critical missing data. Patients in the NTG group had the anesthetic management and NTG treatment according to the protocol described earlier. One to two controls were sampled according to NTG subject, matched on age (±5 years), sex, surgery, and surgeon. Patients in the control group were treated according to the old NTG protocol (an infusion rate of 1–3 mg·h−1) and received a total dosage of NTG <0.5 mg·kg−1 during surgery.

2.6. Outcome measurement

Cerebral saturations were recorded before induction (baseline), after induction, before bypass, 0, 30, 60, 90, 120, 150, and 180 minutes after bypass, before the end of bypass, 30 minutes after the end of bypass, and at the end of surgery. Cerebral desaturation was defined as a relative decrease in regional cerebral oxygen saturation to <80% of the preoperative baseline.

Serum creatinine concentrations were collected at the time point of preoperative baseline, postoperative day (POD) 0 to POD 4 on a daily basis. Acute kidney risk and injury were defined by RIFLE classification,4 namely an increase in serum creatinine 1.5 to 2.0 and 2.0 to 3.0 times baseline, respectively. Creatinine clearance rates before and after the operation were calculated with the Cockcroft-Gault equation.15

Intraoperative hemodynamic parameters were collected, including MAP, heart rate, and body temperature before anesthetic induction, 30 minutes after CPB, 30 minutes after weaning from CPB. Hematocrit levels were collected from arterial blood gas tests at the time of postinduction (baseline), 15 minutes before cessation of CPB, and 30 minutes after cessation of CPB. Pulmonary artery catheterization was routinely performed with continuous cardiac output monitoring after anesthetic induction in cardiac surgical patients. The values of CI, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) were collected at the time of baseline, 30 minutes after the end of bypass, and 4 hours after the arrival of ICU.

Postoperative data included the urine output during the first 24 hours of ICU stay, time to extubation, ICU stay, and postoperative hospital stay. In addition, major complications were also recorded, including acute kidney risk, AKI and RRT, new-onset stroke after surgeries, reoperation within 24 hours, readmission due to cardiogenic causes within 3 months, and in-hospital mortality. Postoperative stroke was based on the brain imaging studies, including computed tomography or magnetic resonance imaging and defined as an event within postoperative 2 weeks. The inotropic score was calculated according the following formula: dopamine in µg·kg−1·min−1 + dobutamine in µg·kg−1·min−1 + milrinone in µg·kg−1·min−1 × 10 + epinephrine in µg·kg−1·min−1 × 10. Low-dose dopamine was defined as <3 µg·kg−1·min−1; dobutamine and levosimendan were considered as other inotropic agents. Radiocontrast agents were considered if used within 72 hours before surgery.
2.7. Statistical analysis
Comparisons between the two groups were done with a Pearson’s χ2 test or Fisher’s exact test for categorical variables and two sample t test or Mann-Whitney U test for continuous variables as appropriate. Propensity score method was used to compensate for the potential difference in baseline attributes between groups and diminish the interaction effect of other variables. The propensity score was obtained by using a logistic regression model, with the addition or omission of high-dose NTG as the dependent variable and all baseline characteristics as independent variables (Appendix 1). The propensity score was then used as the only confounding variable, in association with added or omitted high-dose NTG, to estimate the effect of high-dose NTG on the outcomes. A p < 0.05 was considered significant. All statistical analyses were conducted with SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Scientific graphing was performed with Prism version 6.00 (GraphPad Software Inc., San Diego, CA, USA).

3. RESULTS
In the timeframe of the study, 239 patients were available after meeting the selection criteria. In the NTG group, 96 patients (40.2%) received NTG with a total dosage of >0.5 mg·kg−1 during cardiac surgery. In the control group, 43 patients (18.0%) were given NTG with a total dosage of <0.5 mg·kg−1, and 100 patients (41.8%) had no infusion of NTG during cardiac surgery.

There was no significant difference in the patients’ attributes between the two groups (Table 1). The peak NTG infusion rates during rewarming period were median 20 (range 5-40) mg·h−1 in the NTG group and 0 (0-10) mg·h−1 in the control group. When dividing the patients into three groups, high-dose NTG group (with a total dosage of NTG > 0 and < 0.5 mg·kg−1), low-dose NTG group (with a total dosage of NTG > 0 and < 0.5 mg·kg−1) and no NTG group, their baseline characteristics were shown in Appendix 2.

The NTG group had significantly lower MAP during (50 ± 10 versus 57 ± 11 mmHg; p < 0.001) and after CPB (59 ± 8 versus 65 ± 11 mmHg; p < 0.001) compared with control group (Figure 1). Besides, patients in the NTG group had lower hematocrit levels during (25.5 ± 3.4 versus 26.9 ± 3.0%; p < 0.001) and after CPB (27.2 ± 3.7 versus 29.2 ± 3.2%; p < 0.001) than in the control group (Figure 2). There was no significant difference in the CI and SVR values between groups at the time of postby-pass and ICU stay. However, the PVR after CPB was lower in the NTG group, 110 ± 66 versus 181 ± 139 dynes·s·cm−5 (p = 0.044) (Table 2). The effect of high-dose NTG on the hemodynamic change was similar when dividing the patients into three groups (Appendix 3).

The risk of left-sided cerebral desaturation was 23.9% versus 38.5%, p = 0.023, and right-sided cerebral desaturation 28.1% versus 35.7% in the NTG and control groups, respectively. NTG subjects had fewer transfusions of fresh frozen plasma (FFP) [0 (0-8) versus 2 (0-12) units FFP; p < 0.001] than in the control group. NTG subjects had less perioperative fluid intake (2206 ± 547 versus 2546 ± 841 ml; p = 0.003) and less intraoperative inotrope support, including dopamine (32.3% versus 90.9%; p < 0.001), epinephrine (6.3% versus 59.4%; p < 0.001), norepinephrine (6.3% versus 59.4%; p < 0.001), and other inotropes (2.1% versus 18.9%; p < 0.001) (Table 3, Appendix 4).

The postoperative peak value of serum creatinine was 1.37 ± 0.65 versus 1.47 ± 0.78 mg·dl−1, change of serum creatinine 35.8 ± 38.3 versus 39.5 ± 38.1%, the incidence of acute kidney injury risk 15.6% versus 19.6% and injury 7.3% versus 8.4%, and RRT 1.0% versus 3.5% in the NTG and control groups, respectively. The postoperative inotropic scores were significantly lower in the NTG group [0 (0-26) versus 4.0 (0-52), respectively; p = 0.001]. The risk of major complications was 2.1% versus 6.3% in new-onset stroke, 4.2% versus 4.9% in reoperation, 4.2% versus 10.5% in readmission, and 1.0% versus 7.0% in in-hospital mortality in the NTG and control groups, respectively (Table 4, Appendix 5). Among the cases with stroke, none and five patients had hyperperfusion-type
watershed or lacunar infarction in the NTG and control groups, respectively.

4. DISCUSSION

This study demonstrated that the administration of high-dose NTG during CPB would induce hypotension and hemodilution without elevating the risk of postoperative stroke or renal dysfunction in cardiac surgical patients. The risk of intraoperative cerebral desaturation was lower in the patients treated with high-dose NTG during CPB. Besides, patients treated with high-dose NTG had lower inotropic scores but comparable cardiac performance compared with controls at the arrival of ICU.

Previous studies showed a relative decrease in regional cerebral oxygen saturation of cerebral oximetry to <80% of the preoperative baseline or to absolute levels <50% increase in the risk of adverse postoperative outcomes, including stroke, major organ dysfunction, length of hospital stay, and mortality. In this study, the patients treated with high-dose NTG during CPB had lower risk of intraoperative cerebral desaturation despite their lower MAP and hematocrit levels during and after CPB. The finding is consistent with the prior reports.

Additionally, the NTG subjects had lower risk of postoperative stroke in the study. The finding is against those reported by Gold and colleagues, who demonstrated that patients with controlled minimal MAP of 50 mmHg were associated with higher risk of neurologic complications in contrast to those with targetted MAP of 80 to 100 mmHg. The sample size of the present study cannot provide enough statistical power to detect a difference in postoperative complications. However, our results suggested that the intravenous infusion of NTG as anesthetic strategy to correct episodes of cerebral oxygen desaturation in high-risk patients seems quite promising and warrants further investigations.

Fig. 2. The hematocrit concentration before, during and after cardiopulmonary bypass in the NTG and control groups. Intraoperative hematocrit concentrations were significantly lower in the NTG group (N = 96) than the control group (N = 143) during and after cardiopulmonary bypass (**p < 0.01; ***p < 0.001).

Table 2. Propensity score-adjusted hemodynamic variables

<table>
<thead>
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<th>NTG (N = 96)</th>
<th>Controls (N = 143)</th>
<th>p-value</th>
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<tr>
<td></td>
<td>Pre-bypass</td>
<td>CPB</td>
<td>Post-bypass</td>
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</table>
| MAP, mmHg            | 95 ± 11      | 50 ± 10***         | 59 ± 8***  | 99 ± 17      | 57 ± 11             | 65 ± 11     | <0.01
| HR, bpm              | 79 ± 15      | N/A                | 76 ± 14*   | 80 ± 17      | N/A                 | 84 ± 14     | <0.01
| Temperature, °C      | 36 (34.3–37.2)| 35.6 (32.6–36.9)   | 36 (34.6–37.0)| 36 (34.1–37.4)| 35.4 (33.4–37.2)   | 35.9 (34.4–37.2)| <0.001
| Left ScO2            | 64 ± 13      | 58 ± 10            | 63 ± 10    | 62 ± 12      | 59 ± 11             | 61 ± 11     | <0.001
| Right ScO2           | 63 ± 14      | 57 ± 12            | 62 ± 10    | 60 ± 12      | 58 ± 10             | 59 ± 11     | <0.001
| Hematocrit, %        | 37.8 ± 4.7   | 25.5 ± 3.4**       | 27.2 ± 3.7***| 37.1 ± 4.3   | 26.0 ± 3.0          | 29.2 ± 3.2  | <0.001

Values were mean ± SD or median (range).

ACT = activated clotting time; CI = cardiac index; HR = heart rate; MAP = mean arterial pressure; PVR = pulmonary vascular resistance; ScO2 = cerebral saturation; SVR = systemic vascular resistance.

* p < 0.05; ** p < 0.01; *** p < 0.001.
Table 3

<table>
<thead>
<tr>
<th>Propensity score-adjusted intraoperative parameters</th>
<th>NTG (N = 96)</th>
<th>Control (N = 143)</th>
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<tr>
<td>Cerebral saturations</td>
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<tr>
<td>Lowest Lt ScO2</td>
<td>50 ± 11</td>
<td>49 ± 9</td>
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<tr>
<td>Lt cerebral desaturation</td>
<td>23 (23.9%)*</td>
<td>55 (38.5%)</td>
</tr>
<tr>
<td>Δ Lt cerebral saturation, %</td>
<td>−13.2 ± 14</td>
<td>−15.1 ± 14</td>
</tr>
<tr>
<td>Lowest Rt ScO2</td>
<td>50 ± 11</td>
<td>49 ± 9</td>
</tr>
<tr>
<td>Rt cerebral desaturation</td>
<td>27 (28.1%)</td>
<td>51 (35.7%)</td>
</tr>
<tr>
<td>Δ Rt cerebral saturation, %</td>
<td>−15.0 ± 13</td>
<td>−15.6 ± 13</td>
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<tr>
<td>Vital signs</td>
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<tr>
<td>Pulse pressure, mmHg</td>
<td>64 ± 23</td>
<td>67 ± 25</td>
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<td>Lowest MAP on CPB, %</td>
<td>38 ± 7**</td>
<td>42 ± 8</td>
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<tr>
<td>Lowest HCT on CPB, %</td>
<td>23 ± 4</td>
<td>23 ± 3</td>
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<tr>
<td>Lowest temperature on CPB, °C</td>
<td>32.6 ± 2.1</td>
<td>32.5 ± 2.8</td>
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<td>Fluid management</td>
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<td>Allogeneic pRBC, unit</td>
<td>3.2 ± 2.6</td>
<td>3.9 ± 2.8</td>
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<tr>
<td>FFP, unit</td>
<td>0 (0–8)***</td>
<td>2 (0–12)</td>
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<tr>
<td>Platelet pheresis, unit</td>
<td>0 (0–2)***</td>
<td>0 (0–3)</td>
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<td>Intake fluid, ml</td>
<td>2206 ± 547**</td>
<td>2546 ± 841</td>
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<td>Blood loss, ml</td>
<td>515 ± 272</td>
<td>639 ± 500</td>
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<td>Urine output, ml·kg⁻¹·h⁻¹</td>
<td>2.6 ± 1.4</td>
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<td>Inotropes</td>
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<tr>
<td>Low-dose dopamine</td>
<td>31 (32.3%)**</td>
<td>130 (90.9%)</td>
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<tr>
<td>Epinephrine or norepinephrine</td>
<td>6 (6.3%)*</td>
<td>85 (69.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.1%)*</td>
<td>27 (18.9%)</td>
</tr>
<tr>
<td>Hepatine, U·kg⁻¹</td>
<td>331 ± 58</td>
<td>327 ± 55</td>
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<tr>
<td>Protamine, mg·kg⁻¹</td>
<td>3.2 ± 0.6</td>
<td>3.3 ± 0.7</td>
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</table>

Values were count (percent), mean ± SD or median (range).

*p < 0.05, **p < 0.01, ***p < 0.001.

FFP = fresh frozen plasma; HCT = hematocrit; MAP = mean arterial pressure; pRBC = packed red blood cells; ScO2 = cerebral saturation.

In conclusion, the infusion of high-dose nitroglycerin initiating at rewarming of CPB and throughout the post-bypass interval may induce hypotension and hemodilution. Cerebral saturation and renal function were well maintained without increasing the risk of new-onset stroke or RRT after cardiac surgery with CPB.

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A12.

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